Exhibit 23

Epithelial ovarian cancer

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Epithelial ovarian cancer generally presents at an advanced stage and is the most common cause of gynaecological cancer death. Treatment requires expert multidisciplinary care. Population-based screening has been ineffective, but new approaches for early diagnosis and prevention that leverage molecular genomics are in development. Initial therapy includes surgery and adjuvant therapy. Epithelial ovarian cancer is composed of distinct histological subtypes with unique genomic characteristics, which are improving the precision and effectiveness of therapy, allowing discovery of predictors of response such as mutations in breast cancer susceptibility genes *BRCA1* and *BRCA2*, and homologous recombination deficiency for DNA damage response pathway inhibitors or resistance (cyclin E1). Rapidly evolving techniques to measure genomic changes in tumour and blood allow for assessment of sensitivity and emergence of resistance to therapy, and might be accurate indicators of residual disease. Recurrence is usually incurable, and patient symptom control and quality of life are key considerations at this stage. Treatments for recurrence have to be designed from a patient's perspective and incorporate meaningful measures of benefit. Urgent progress is needed to develop evidence and consensus-based treatment guidelines for each subgroup, and requires close international cooperation in conducting clinical trials through academic research groups such as the Gynecologic Cancer Intergroup.

Epidemiology and risk factors

Since the last seminar publication 4 years ago,[1] there have been major improvements in the understanding of the biology of invasive epithelial ovarian cancer (EOC) (figure 1), and this knowledge has led to changes in clinical practice. This Seminar will summarise the current optimal evidence-based approach to management of EOC. EOC is the most lethal gynaecological cancer. Annually worldwide, 230 000 women will be diagnosed and 150 000 will die.[2] It represents the seventh most commonly diagnosed cancer among women in the world with 46% survival 5 years after the diagnosis.[3] One of the main factors contributing to the high death-to-incidence rate is the advanced stage of the disease at the time of diagnosis. Late stage presentation has a 5-year relative survival rate of 29%, by contrast with 92% for early-stage disease.[4] About 75% of patients are diagnosed at an advanced stage because of the asymptomatic nature of EOC. Genomic predisposition to EOC is now well recognised in up to 15% of affected women. Breast cancer susceptibility genes *BRCA1* and *BRCA2* have been identified as causative genes involved in 65–75% of hereditary EOC. Deleterious mutations in *BRCA1* and *BRCA2,* and other double-strand DNA break repair genes, are largely associated with the high-grade serous EOC subtype susceptibility. Lynch syndrome, an autosomal dominant hereditary cancer family syndrome, accounts for 10–15% of hereditary EOC,[5,6] and is typically associated with endometrioid or clear-cell tumours.[4] Other genetic syndromes include Peutz-Jegher and rare disorders, such as Gorlin syndrome.[7] Risk factors for EOC include the number of lifetime ovulations (absence of pregnancy, early age of menarche, and late age at menopause), family history of EOC, smoking, benign gynaecological conditions (including endometriosis, polycystic ovary syndrome, and pelvic inflammatory disease),[4] and potentially use of talcum powder.[8]

Screening

Considerable efforts have been made to implement screening of the general population to diagnose EOC early, but there is no approved strategy.[9] The UKCTOCS trial (NCT00058032), a randomised controlled trial of over 200 000 women assessing annual multimodal screening with serum cancer antigen (CA125), did not identify significant mortality reduction when the risk for ovarian cancer algorithm (ROCA) was used, versus annual transvaginal ultrasound screening, versus no screening. Further follow-up is underway to assess late benefit (7–14 years after an index screening event) in post-menopausal women because of a significant stage shift in women diagnosed with invasive ovarian, tubal, or peritoneal cancer with multimodal screening compared to no screening.[10] Additional biomarker combinations such as human epididymis protein 4, a glycoprotein secreted by the Mullerian epithelia of the female reproductive tract, have been tested with CA125,[11] but further studies are required. A study[12] screened 4348 women with 10% or higher lifetime risk of ovarian or fallopian tube cancer using ROCA and transvaginal sonography, showing evidence for stage shift, with 53% of diagnoses made during the trial being early-stage cancers, compared with only 6% of early-stage cancers detected more than 1 year after the trial screening finished. Longer follow-up will determine the effect of this strategy on survival. The recommendation for unaffected individuals with a high familial risk of ovarian cancer is risk-reducing salpingo-oophorectomy by an age that depends on their individual genetic predisposition. Efforts are also underway to improve genomic screening strategy.[13]

Diagnosis

EOC symptoms are not specific and include abdominal bloating, early satiety, nausea, abdominal distension, change in bowel function, urinary symptoms, back pain, fatigue, and loss of weight, which typically present months

before diagnosis.[14] Initial investigations include the measurement of CA125 concentrations and pelvic ultrasound. To accurately define EOC extension, further imaging should include chest and abdomen or pelvis CTs for staging, and potentially a pelvic MRI. Optimal staging is surgical and includes total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, inspection of peritoneal surfaces with biopsy or removal of any suspicious areas, and para-aortic and pelvic lymph node dissection. Surgery should be done by a trained gynaecological oncology surgeon with the goal of no residual disease. The staging procedure will establish the surgical stage, conventionally with International Federation of Gynecology and Obstetrics (FIGO) staging of ovarian cancer or with tumour, node, metastasis classifications by the American Joint Committee on Cancer.[15,16]

Pathological diagnosis on tumour tissue is essential because ovarian cancer has different histological subtypes with different treatment approaches. Over the past decade it has become clear that EOC consists of a number of diseases (figure 2) with distinct precursor lesions, tissues of origin, molecular biology, clinical presentation, chemosensitivity, and patient outcome.

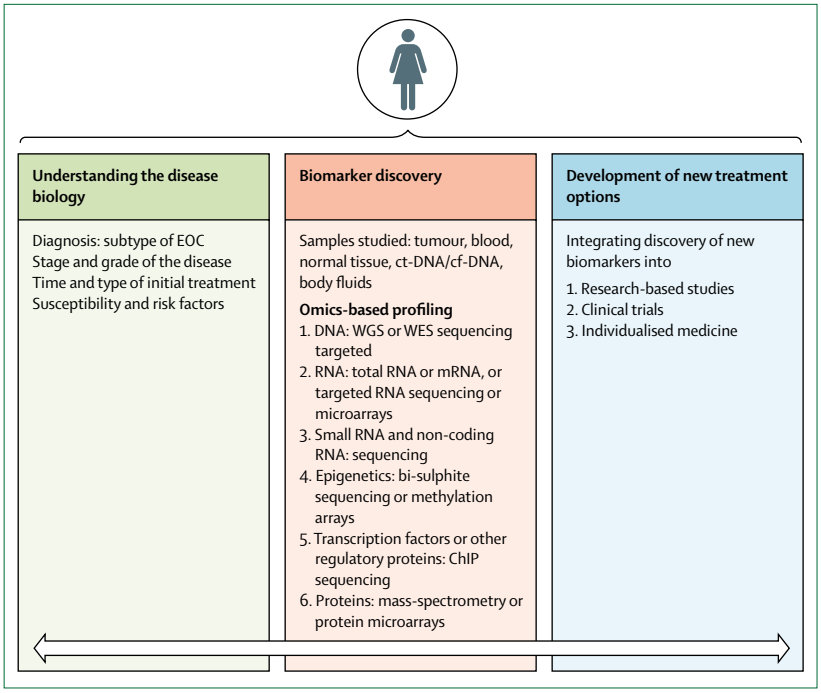

Figure 1: **Evolving management strategies based on disease biology and molecular profiling of novel biospecimens**
Integrated approach combining understanding of ovarian cancer disease biology and evolution, and application of novel omics-based technologies as a part of research-based studies or clinical trials. EOC=epithelial ovarian cancer. ct-DNA=circulating tumour DNA. cf-DNA=circulating free DNA. WGS=whole genome sequencing. WES=whole exome sequencing. ChIP=chromatin immunoprecipitation.

First-line treatment approach

Surgery

Primary debulking surgery (PDS) followed by chemotherapy has become the standard of care in advanced EOC since the 1980s, despite few upfront randomised trials defining its actual benefit.[17] No residual tumour (R0) after PDS is the most important prognostic factor for survival.[18] Two randomised clinical trials comparing PDS and chemotherapy with neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) showed similar survival with a low operative morbidity when NACT and IDS were used.[19,20] Both trials have been criticised for their low R0 rates and low survival rates. However, it should be noted that most of the patients had extensive stage IIIC or IV disease. To help the debate, the TRUST trial (NCT02828618) randomising NACT versus PDS in advanced EOC is ongoing in selected centres with 50% or more R0 rates and the results will be available in a few years. The choice between PDS and chemotherapy or NACT and IDS is controversial.[21] Further research is needed on how to select patients for PDS or NACT, including better and validated imaging or laparoscopic scoring systems and algorithms to predict operative morbidity.

A guideline for selecting patients with FIGO stage IIIC and IV disease for PDS or NACT followed by IDS is presented in the table.[22] The algorithm and guideline are based on the EORTC 55971 randomised trial,[20] showing that patients with stage IIIC disease and small metastases (<5 cm) had better overall survival with PDS whereas patients with stage IV disease had better survival with NACT. At the time of surgery, all visible or palpable tumour must be removed at PDS and IDS.[18,20] For decades the role of a full pelvic and para-aortic lymphadenectomy in advanced EOC has been advocated.[25] However, a randomised study from the AGO-OVAR trial,[26] has shown that systematic pelvic and para-aortic lymphadenectomy in patients with advanced EOC with both intra-abdominal complete resection and clinically negative lymph nodes does not improve overall or progression-free survival (PFS).

In patients with stage IA low grade disease opting for fertility conservation surgery, the uterus and contralateral ovary can be left in place pending pathology review of the removed tissues and further discussion with the patient. The selection of patients for fertility preservation requires very careful consideration of the risks and benefits between the surgical oncologist and patient. The likelihood of cure is high for women with stage IA disease, but residual disease and subsequent recurrence are associated with low likelihood of salvage. Pathological differences greatly affect the potential for conservative surgery, and this option is best reserved for women with well-differentiated or low-grade, stage IA disease.[27]

Systemic therapy

The treatment guidelines for EOC have largely been driven by high grade serous ovarian cancer (HGSOC), and first-line therapy has largely been established on the basis of this subgroup. Randomised clinical trials in early-stage disease have been challenging to do because

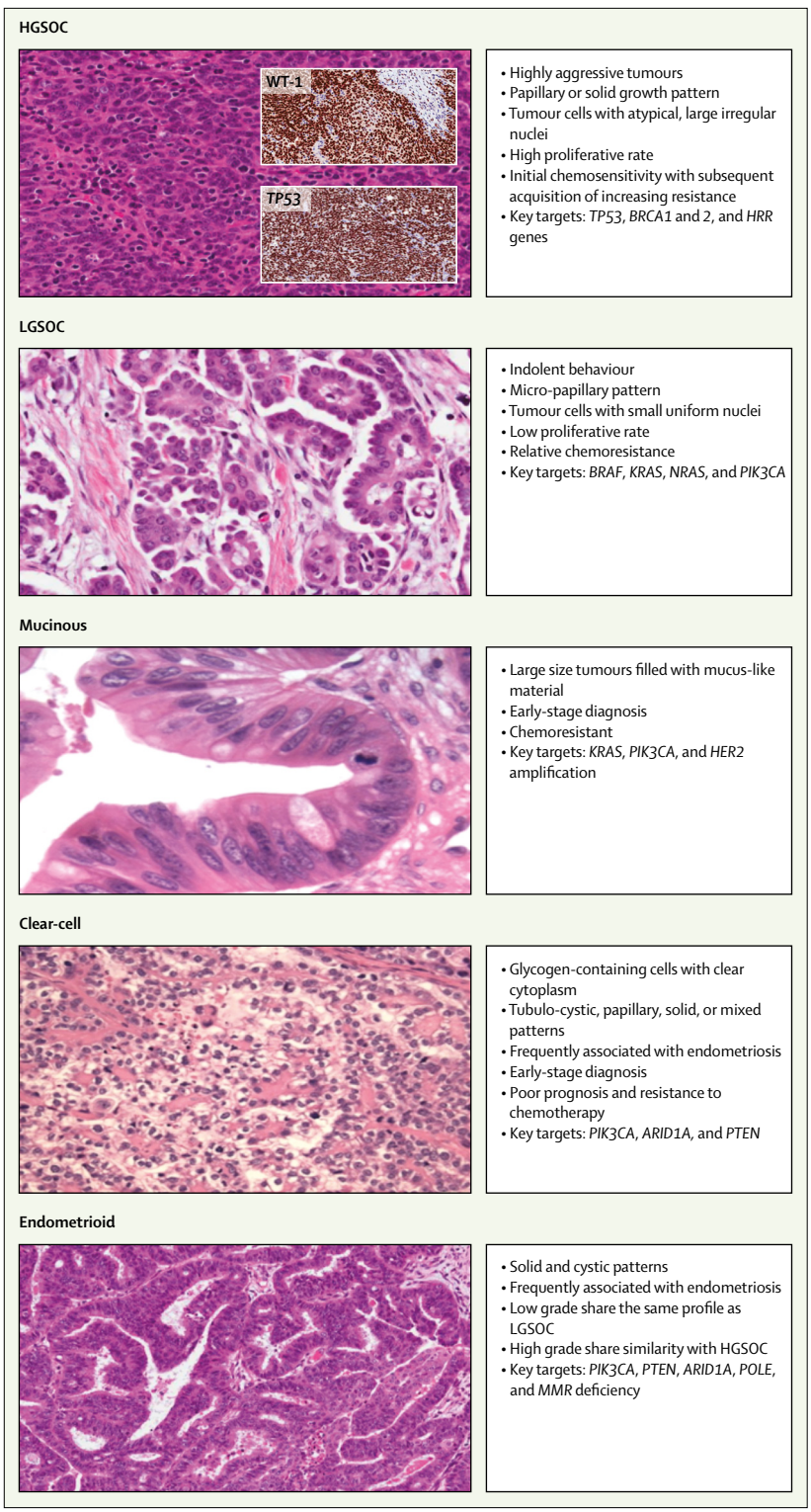

Figure 2: **Different histological subtypes of epithelial ovarian cancers and their salient features**
P53 and WT1 staining in HGSOC is shown. The magnifications for H and E range between 50–400×, whereas immunohistochemistry is 50×. HGSOC=high-grade serous ovarian carcinoma. LGSOC=low-grade serous ovarian carcinoma.

a minority of patients present early. The ICON[28] and ACTION[29] randomised trials support the use of adjuvant chemotherapy in early-stage disease, with carboplatin or cisplatin and paclitaxel, with level Ia evidence.[28–33] Subset analyses raised the question of avoiding chemotherapy in well-staged patients with early-stage disease, but this finding should be considered as exploratory.[34] The question of adjuvant therapy for early-stage disease can be discussed on the basis of histology subtype and grade.[35] The GOG157 trial[36] compared three versus six cycles of adjuvant paclitaxel and carboplatin, but was powered to detect a 50% decrease in the recurrence rate at 5 years; there was no difference in the groups, perhaps supporting a reduction in the number of cycles, with reduced toxicity in well-staged patients. However, the standard recommendation in practice is six cycles of platinum adjuvant therapy.

Intravenous administration of carboplatin (area under the curve 5–6) and paclitaxel (175 mg/m² over 3 h) every 3 weeks is the standard first-line chemotherapy drug treatment for advanced-stage EOC.[37] Weekly intravenous paclitaxel administration has been investigated and might be an alternative to paclitaxel in combination with intravenous carboplatin administrated once every 3 weeks. In the Japanese Gynecologic Oncology Group 3016 study, 631 women with stage II–IV EOC were randomised between carboplatin AUC 6 with paclitaxel 180 mg/m² every 3 weeks, and carboplatin AUC 6 every 3 weeks with weekly paclitaxel 80 mg/m². A sustained significant improvement in PFS and overall survival for patients receiving dose-dense therapy compared with conventional treatment was reported.[38] However, a benefit in PFS was not seen in three other trials with weekly paclitaxel,[39–41] possibly because of pharmacogenomic influences because the initial JGOG 3016 trial[38] (NCT00226915) was in a Japanese population whereas the subsequent trials[39–41] were predominantly in white populations.

Two randomised trials, GOG218[42] and ICON7,[43] showed a significantly increased PFS, but not overall survival with the addition of the anti-angiogenesis inhibitor bevacizumab (directed against vascular endothelial growth factor), to paclitaxel every 3 weeks and carboplatin followed by maintenance bevacizumab. In a pre-planned analysis of the ICON7 study,[43] the addition of bevacizumab in women at high risk of progression (stage III disease with >1 cm residual disease following PDS, and inoperable patients with stage III and IV disease), significantly improved the estimated median PFS (10·5 months with standard therapy *vs* 15·9 months with bevacizumab [hazard ratio (HR) 0·68; 95% CI, 0·55–0·85; p<0·001] and median overall survival (28·8 *vs* 36·6 months [0·64; 0·48–0·85; p=0·002]). These findings led to the addition of bevacizumab to paclitaxel and carboplatin every 3 weeks as standard of care in this high-risk population in many countries. The AGO trials group exploring 15 versus 30 cycles of chemotherapy[44–46] will confirm

	Both Leuven and Essen criteria	Essen criteria only	Leuven criteria only
Diagnosis	Biopsy with histologically proven epithelial ovarian, tubal or peritoneal cancer FIGO stage IIIC-IV	..	Fine needle aspiration proving the presence of carcinoma cells in patients with a suspicious pelvic mass if CA125 (KU/L)/CEA (ng/mL) ratio is >25; if the serum CA125/CEA ratio is ≤25, imaging or endoscopy is obligatory to exclude a primary gastric, colon, or breast carcinoma
Abdominal metastases	Involvement of the superior mesenteric artery; diffuse deep infiltration of the root of the small bowel; diffuse and confluent carcinomatosis of the stomach or small bowel involving such large parts that resection would lead to a short bowel syndrome or a total gastrectomy	Multiple parenchymatous liver metastases in both lobes; tumour involving large parts of the pancreas (not limited to tail) or the duodenum or both; tumour infiltrating the vessels of the ligamentum hepatoduodenale or truncus coeliacus	Intrahepatic metastases; infiltration of the duodenum or pancreas, or the large vessels of the ligamentum hepatoduodenale, truncus coeliacus, or behind the porta hepatis
Extra-abdominal metastases	..	Not fully resectable metastases (eg, multiple parenchymal lung metastases*, non-resectable lymph node metastases, and brain metastases)	All excluding: resectable inguinal lymph nodes, solitary resectable retrocrual or paracardial nodes, and pleural fluid containing cytologically malignant cells without proof of the presence of pleural tumours
Patients' characteristics	Impaired performance status and comorbidity not allowing a maximal surgical effort to achieve a complete resection; patients' non-acceptance of potential supportive measures such as blood transfusions or temporary stoma	..	..
Criteria for interval debulking	..	Upfront surgical effort in an institution without specialised expert availability, surgical skills competency, and adequate infrastructure; barrier for initial surgery has disappeared (eg, improved medical condition); interval debulking is not indicated, if the reason for primary chemotherapy was tumour growth pattern, diagnosed during open surgery by an experienced gynaecological oncologist under optimal circumstances (as in GOG study 152[23])	No progressive disease, and in case of extra-abdominal disease at diagnosis the extra-abdominal disease should be in complete response to treatment or resectable; performance status and comorbidity allowing a maximal surgical effort resulting in no residual diseases

Adapted with permission from Vergote I, et al.[24] FIGO=International Federation of Gynaecology and Obstetrics. *Preferably histologically proven.

Table: **Leuven and Essen criteria for considering neoadjuvant chemotherapy and interval debulking surgery in FIGO stage IIIC and IV ovarian carcinoma**

or refute the hypothesis from the ICON7[43] and ROSIA[44] trials that benefit of bevacizumab is related to the maintenance duration.

The use of intraperitoneal cisplatin and paclitaxel has resulted in a survival advantage in several trials in patients with less than 1 cm residual tumour after PDS.[47–49] These trials have been criticised because they were hampered by outdated control groups, experimental intraperitoneal chemotherapy groups, various changes (eg, different dose, dose-dense regimens), and higher toxicity.[50] The role of intraperitoneal therapy has come into question with the GOG252 study, assessing dose-dense intravenous treatment versus intraperitoneal therapy with the addition of bevacizumab, of which intraperitoneal therapy with bevacizumab did not show any benefit in PFS for patients with FIGO stage 3 disease and less than 1 cm residual tumour following PDS.[51] These findings seem to show that dose for dose, there is no advantage of intraperitoneal chemotherapy over intravenous chemotherapy. Studies that were associated with benefit of intraperitoneal chemotherapy used intraperitoneal cisplatin at 100 mg/m² and were associated with a higher incidence of toxicity.

Hyperthermic intraperitoneal chemotherapy (HIPEC) until 2017 had no proven benefit in EOC.[52] However, in 2017, two randomised studies from Dutch[53] and Korean[54] groups used HIPEC at the time of IDS after NACT.[52–54] The Dutch trial reported significant advantage for the HIPEC group, which was not observed in the Korean trial. In the Dutch trial, the median recurrence-free survival was 10·7 months in the surgery group and 14·2 months in the surgery with HIPEC group, and the median overall survival was 33·9 months in the surgery group versus 45·7 months in the surgery with HIPEC group. In women who received NACT in the Korean trial, the median PFS was 20 months for the HIPEC group and 19 months for the control group (log-rank test, p=0·137), and the median overall survival was 54 months for the HIPEC group and 51 months for the control group (log-rank test, p=0·407). These trials were small and resulted in higher toxicity when HIPEC was used, and should be confirmed before HIPEC can be used as standard of care.[55] The key question of whether benefit is related to an additional intraperitoneal cycle of therapy or the potential association with hyperthermia is going to be evaluated in a prospective trial (Dr Sudeep Gupta, Tata Memorial Centre, Mumbai, personal communication).

Follow-up

Follow-up might identify disease recurrence earlier, but there are no clear guidelines on the type and frequency; regular physical examination is generally recommended. The earliest indication of recurrent disease might be CA125 in patients where this has been a marker of disease. With neither radiological nor clinical evidence of disease, recurrence can be defined by the rise of more

than twice the upper limit of normal (ULN is 35 U/mL) for patients with normal baseline CA125 levels, or for those whose CA125 levels have normalised during treatment, or CA125 level more than twice nadir value (on two successive occasions) for patients whose CA125 levels have not normalised. The question of value from close monitoring to detect recurrence early remains, because no survival benefit was observed with early treatment of relapse on the basis of increased CA125 alone.[56] This finding might have been because of the paucity of effective therapeutic options at recurrence, or a limitation of the study, which was underpowered to detect a potential survival benefit in patients eligible for secondary cytoreduction. Although early detection might not have survival advantage, it does allow for exploration of treatment options, including surgery or experimental therapies, which have led to regular follow-up after completion of primary therapy.

See Online for appendix

CT scans can detect an asymptomatic recurrence and should be systematically done to establish a baseline before starting new lines of therapy. Several studies have demonstrated the use of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET and ^{18}F-FDG PET integrated with CT for early detection of recurrent EOC, and MRI in the evaluation of patients with recurrent EOC and its potential role of prediction of optimal secondary debulking surgery (SDS).[57]

Recurrence

Recurrence is incurable in about 75% of women who present with advanced disease. A functional algorithm using the platinum-free interval to select subsequent therapy has been a simple and remarkably effective way of choosing therapy and inferring prognosis for the last 30 years. In November, 2015, the Gynecologic Cancer Intergroup redefined the conventional practice of using platinum-free interval to categorise patients as platinum-sensitive or platinum-resistant, and replaced this practice by a therapy-free interval, with the cutoff at 6 months.[58]

At the time of relapse, SDS should be considered for appropriate patients.[59] AGO-OVAR developed the Descriptive Evaluation of preoperative Selection KriTeria for OPerability (DESKTOP) score as a predictive algorithm of effective SDS.[60] Patients with the first recurrence and a platinum-free interval of more than 6 months (platinum-sensitive) EOC have a positive DESKTOP score when accompanied by good performance status (Eastern Cooperative Oncology Group [ECOG] scale 0), complete resection during first-line therapy, and ascites of less than 500 mL; these patients have a significantly better PFS when undergoing SDS followed by chemotherapy, versus chemotherapy alone.[61] A positive DESKTOP score predicted the probability of complete resection in more than two out of three patients with 95% accuracy.[60] The Tian Risk model,[62] which is also based on the factors affecting the SDS surgical outcome, utilises six factors predicting complete cytoreduction: FIGO stage (I and II *vs* III and IV), residual disease after primary cytoreduction (0 mm *vs* >0 mm), PFS (<16 months *vs* ≥16 months), ECOG performance status (0–1 *vs* 2–3), CA125 (≤ 105 U/mL *vs* >105 U/mL), and ascites at recurrence (absent *vs* present). Memorial Sloan Kettering criteria are also used to predict for complete gross resection in secondary cytoreductive surgery in EOC.[63]

If there is no surgical option, systemic therapy is used to control the disease for as long as possible. Several clinical trials have changed the options for care and remain an active area of investigation to overcome systemic therapy resistance. The type of treatment will be based on patient, time of recurrence, tumour histology, and disease biology. Given that HGSOC is the most common type of EOC, we will focus on this specific group. The other histology subtypes including low-grade serous, clear-cell, endometrioid, and mucinous are described in the appendix.

High grade serous ovarian cancer

Epidemiology and origin

HGSOC is the most common type of EOC, accounting for 75% of all EOC. HGSOC pathogenesis has evolved from the notion that it develops from the ovarian epithelium to the epithelium of the distal fallopian tube.[64] Serous tubal intraepithelial carcinomas are suspected to be the precursor lesion of some HGSOC, with molecular features involving mutations in *TP53* as an early event.[65] Bilateral salpingo oophorectomy is the standard of care for risk reduction in *BRCA1* and *BRCA2* carriers. Prevention studies are assessing bilateral salpingectomy with delayed oophorectomy in women with high risk.[66]

Hereditary susceptibility

As 15–20% of HGSOC patients have germline *BRCA1* or *BRCA2* mutations, diagnosis should trigger genetic testing.[67] The confirmation of germline mutation in a patient should also lead to offering germline testing offered to first degree relatives to identify carriers who might benefit from screening. In family predisposition studies, the cumulative risks of EOC by the age of 80 years are estimated to be 44% in *BRCA1* and 17% in *BRCA2* mutation carriers.[68] Female *BRCA1* or *BRCA2* mutation carriers should consider prophylactic risk-reduction surgery after childbearing and around age 38 years, when the risk of EOC begins to increase because this surgery is the only proven risk-reducing strategy.[69] Other genes of moderate penetrance involve *RAD51C, RAD51D,* and *BRIP1*; although their individual mutation frequency is uncommon (<1% each), cumulatively they might be responsible for about 5% of EOC. Therefore, genetic testing for women with HGSOC includes *BRCA1, BRCA2,* and other susceptibility genes.[70] Studies are also evaluating early detection of *TP53* in blood or uterine lavage as a potential genomic screen.[71,72]

Pathology

The growth pattern of HGSOC is heterogeneous, involving large papillae, being glandular, solid and occasionally micropapillary with frequent necrosis; it is defined by its high-grade nuclei and mitotic index[73] (figure 2). Immunohistochemistry stain is abnormal for p53, diffusely expressed for p16, and elevated for Ki67; additional markers include ER, PR, WT-1, and PAX8.

Molecular abnormality

HGSOC is characterised by gain of function mutations in *TP53*,[73] high-frequency somatic copy number alterations, and whole genome duplications.[74] HGSOC is associated with lower prevalence but recurrent somatic mutations in *NF1, BRCA1, BRCA2, RB1,* and *CDK12* [74] in around 5–8% of tumours (figure 3). HGSOC is also characterised with frequent DNA gains and losses, making this cancer chromosomally unstable, with potential for acquired chemoresistance (*CCNE1* amplification).[75] Heterozygous and homozygous loss is an important mechanism for inactivation of tumour suppressors.[76] Genomic analyses show that homologous recombination is defective in nearly half of HGSOC.[74] This homologous recombination deficiency (HRD) is a key determinant of platinum sensitivity in HGSOC and has been exploited for treatment with poly (ADP-ribose) polymerase inhibitors (PARPi).[77] Myriad HRD test and Foundation Medicine loss-of-heterozygosity assay assess HRD in tumours as a potential predictive biomarker for PARPi therapy. Molecularly, HGSOC might be stratified into four different prognostic subtypes (C1–mesenchymal, C2–immune, C4–differentiated, and C5–proliferative)[74,78,79] and potentially seven copy-number signatures;[80] both stratification methods require prospective validation to be used in a predictive way.

Treatment

In the platinum-sensitive recurrence setting, if surgery is not indicated, a re-challenge with platinum doublet chemotherapy is standard, with six to eight cycles of therapy.[81–84] Maintenance strategies have been developed to delay subsequent progression and possibly improve overall survival.[85] Phase 3 trials with bevacizumab showed a significant benefit for maintenance on disease control rate.[86,87] In the OCEANS trial,[86] the addition of bevacizumab to carboplatin and gemcitabine increased median PFS from 8·4 months to 12·4 months (HR 0·484; 95% CI, 0·388–0·605; log-rank p<0·0001). GOG213 confirmed the benefit of adding bevacizumab to carboplatin and paclitaxel with improvement in overall survival after correcting for platinum-free interval (0·823; 0·680–0·996; p=0·0447).[87]

A re-challenge with chemotherapy plus bevacizumab for platinum-sensitive recurrence and patients who previously received bevacizumab as first line showed a clinical benefit with a median PFS from 8·8 months to 11·8 months without and with bevacizumab, respectively (0·51, 0·41–0·64, p<0·001) but no significant difference in overall survival.[88] The benefit of adding and continuing an anti-angiogenic agent was further confirmed with cediranib.[89]

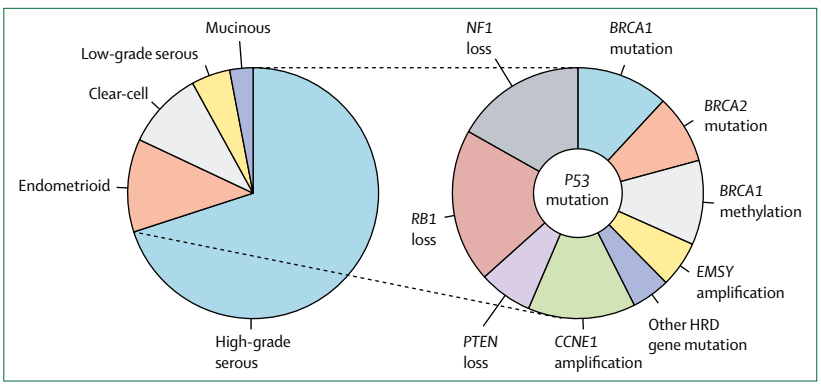

Figure 3: **Common molecular abnormalities in ovarian cancer**
Left side shows the breakdown of epithelial ovarian cancer according to histological subtype. Right side shows the breakdown of the main molecular abnormalities that are thought to drive high-grade serous ovarian tumours (*P53* mutation is an almost ubiquitous finding). *EMSY=EMSY, BRCA2* Interacting Transcriptional Repressor.

PARPi have been successfully implemented in recurrent HGSOC by leveraging inherent defects in DNA repair mechanisms present in around 50% of HGSOC because of mutations in *BRCA1, BRCA2,* or associated HRD genes, or by functional inactivation through methylation.[74] PARPi have shown remarkable activity as a single agent in women with recurrent disease regardless of *BRCA1* and *BRCA2* mutations, with improved activity in women with *BRCA1* or *BRCA2* mutations and platinum-sensitive disease.[90–93] Olaparib was the first PARPi approved initially for the treatment of advanced EOC in patients carrying germline *BRCA1* or *BRCA2* mutations who have received three or more previous lines of chemotherapy with response rate of 31·1% (95% CI 24·6–38·1).[91,94] In December, 2016, the US Food and Drug Administration (FDA) granted accelerated approval of rucaparib for the treatment of patients with HGSOC carrying deleterious germline or somatic *BRCA1* or *BRCA2* mutations previously treated with two or more lines of chemotherapy[92,95] on the basis of the investigator-assessed objective response rate of 54% (95% CI 44–64), and median duration of response of 9·2 months (6·6–11·7). Olaparib was approved in Europe as maintenance treatment in patients with platinum-sensitive relapsed HGSOC characterised by *BRCA1* or *BRCA2* mutations.[96] Among patients with a *BRCA1* and *BRCA2* mutation, median PFS was significantly longer in the olaparib group than in the placebo group (11·2 months [95% CI 8·3-not calculable] *vs* 4·3 months [3·0–5·4]; HR 0·18 [0·10–0·31]; p<0·0001); for patients with wild-type *BRCA1* and *BRCA2*, the difference was lower (7·4 months [5·5–10·3] *vs* 5·5 months [3·7–5·6]; HR 0·54 [0·34–0·85]; p=0·0075).[97] In women with *BRCA1* or *BRCA2* mutations, the SOLO2 trial[98] confirmed the importance

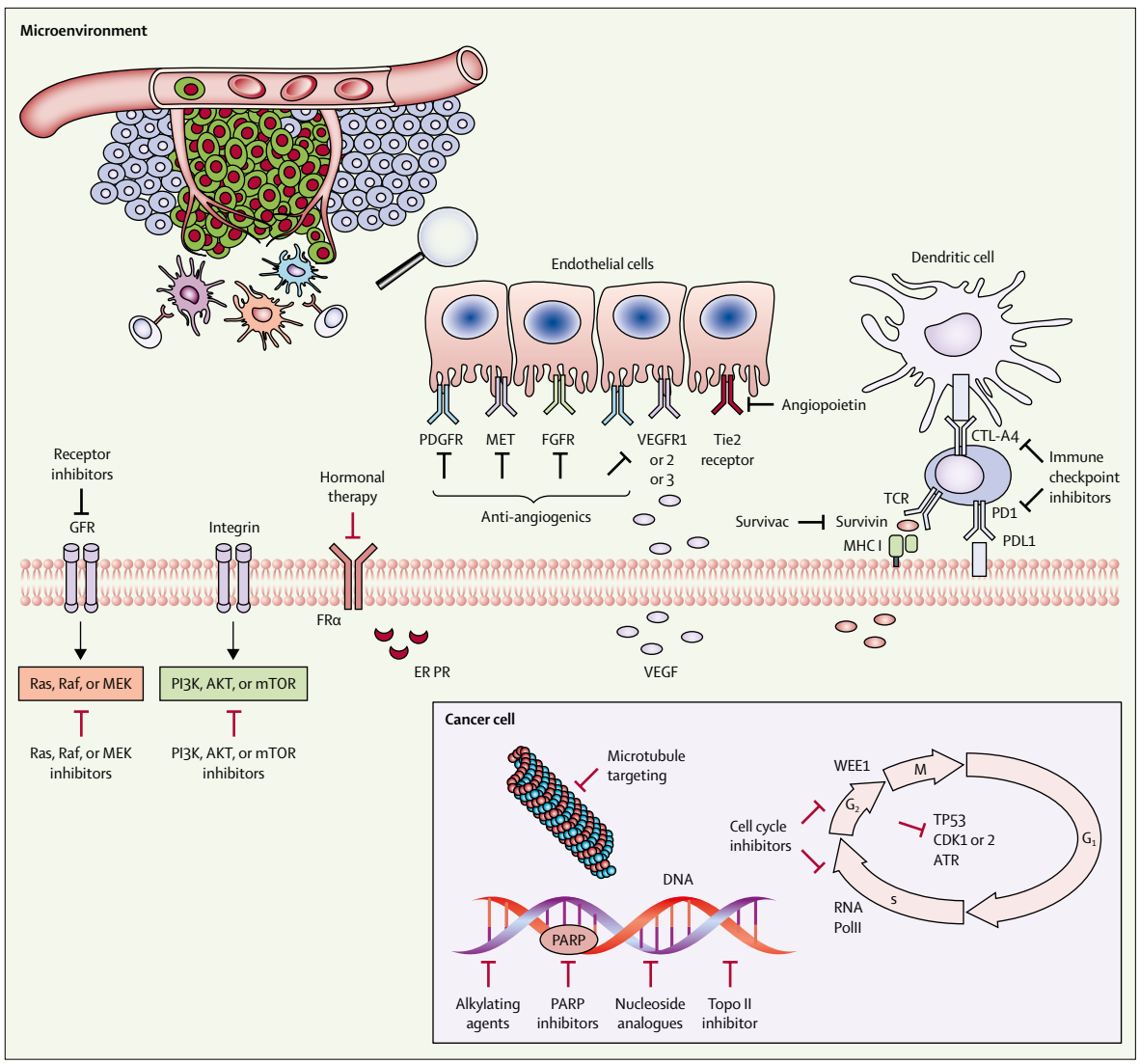

Figure 4: **Different molecular targets and pathways in ovarian cancers currently under investigation for drug development**
The molecular targets could arise from within a cancer cell or from the tumour microenvironment, such as host immune cells or vascular tissue.

of maintenance, which was followed by the FDA's approval of olaparib as maintenance therapy in women with platinum-sensitive disease following response to chemotherapy.

In December, 2018, the FDA approved olaparib for maintenance treatment of BRCA mutated advanced EOC following first-line platinum-based chemotherapy.[99] This approval was given on the basis of the SOLO1 trial[100] (70% lower risk of disease progression or death with olaparib vs placebo). The benefit of maintenance PARPi extends beyond *BRCA1* and *BRCA2* mutations and HRD. Following the results of the phase 3 NOVA study,[101] niraparib received FDA approval as maintenance treatment of patients with platinum-sensitive recurrent EOC who have achieved a complete or partial response following platinum-based chemotherapy regardless of *BRCA* status. Patients treated with niraparib had a significantly longer median PFS than did those given placebo, including 21·0 months versus 5·5 months in the germline *BRCA1* or *BRCA2* cohort (HR 0·27, 95% CI 0·17–0·41), as compared with 12·9 months versus 3·8 months in the non-germline *BRCA1* or *BRCA2* cohort for patients who had tumours with HRD (0·38, 0·24–0·59) and 9·3 months versus 3·9 months in the overall non-germline *BRCA1* or *BRCA2* cohort (0·45, 0·34–0·61; p<0·001 for all three comparisons). The most recent addition to the pharmacopeia has been rucaparib, which showed significant benefit for maintenance therapy following a good response to platinum-based chemotherapy following recurrence.[102] Median PFS in patients with a *BRCA*-mutant carcinoma was 16·6 months (95% CI 13·4–22·9) in the rucaparib group versus 5·4 months (3·4–6·7) in the placebo group (HR 0·23 [95% CI 0·16–0·34]; p<0·0001); in patients

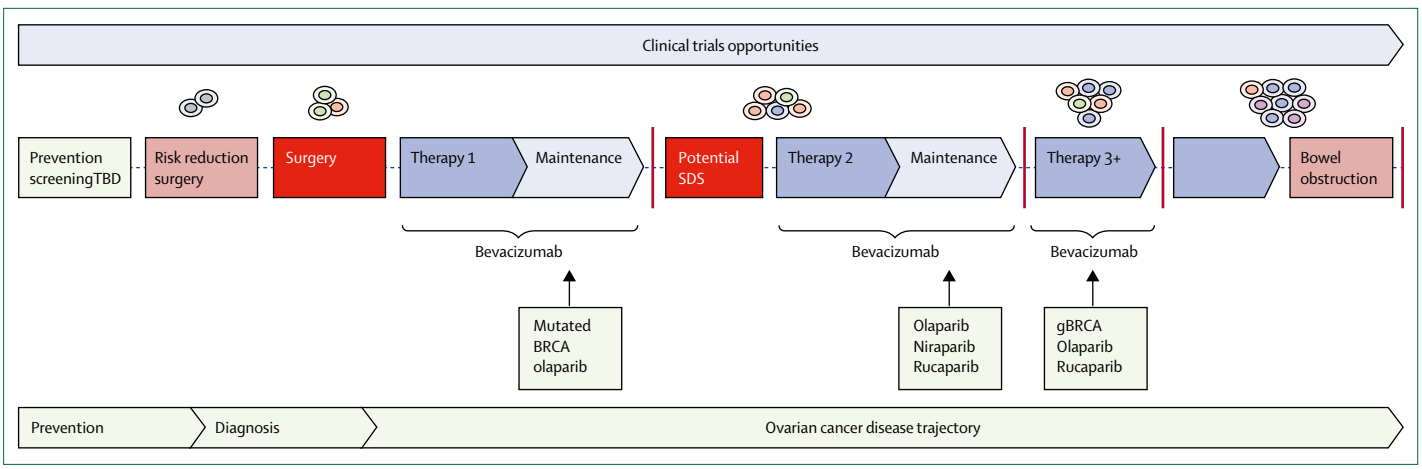

Figure 5: **Disease evolution and treatment opportunities in ovarian cancer**
Combination therapy targeting DNA damage response, cell-cycle, signalling pathway, and tumour microenvironment might be required to control the profound genomic complexity of evolution of HGSOC. Bevacizumab is a vascular endothelial growth factor inhibitor, whereas olaparib, niraparib, and rucaparib are poly ADP-ribose polymerase inhibitors. The vertical red lines represent the time of recurrence. SDS=secondary debulking surgery. TBD=to be determined. HGSOC=high-grade serous ovarian cancer.

with an HRD carcinoma, it was 13·6 months (10·9–16·2) versus 5·4 months (5·1–5·6; HR 0·32 [0·24–0·42]; p<0·0001).

Collectively, the greatest benefit of PARPi as single agent therapy has been observed in women with HGSOC containing deleterious germline or somatic mutations in *BRCA1* or *BRCA2*,[103] followed by women with evidence of HRD; however, biomarkers have not been specific enough to predict benefit. Novel strategies are underway to avoid the use of chemotherapy and involve combination of targeting drugs, such as olaparib and cediranib,[104] regardless of *BRCA1* and *BRCA2* status at the time of platinum-sensitive relapse.

Recurrent disease follows a frequent relapse–response pattern before becoming resistant to treatment. For platinum-resistant disease, various sequential mono-chemotherapies including weekly paclitaxel, liposomal doxorubicin, and gemcitabine are used until subsequent progression or unacceptable toxicity. However, as the expected response rate in the platinum-resistant setting is low (about 10–15%), several trials are investigating new agents to overcome resistance.[105] In the platinum-resistant setting, a phase 3 trial (AURELIA)[106] showed that addition of bevacizumab to various chemotherapy regimens increased the PFS from 3·4 months to 6·7 months (HR 0·48, 95% CI 0·38–0·60; unstratified log-rank p<0·001). An unplanned exploratory subgroup analysis reported that the PFS benefit was greatest in the weekly paclitaxel group, with an improvement from 3·9 months to 10·4 months with addition of bevacizumab.

Patients with refractory disease, defined as progression during the first line of platinum-based chemotherapy, have a very poor prognosis with very low response rate to standard chemotherapy. These patients are often excluded from trials and there is an urgent need to define options for this group.

Future directions

After the approval of anti-angiogenics and PARPi, there is an active interest in combination therapy to overcome resistance. Acquired drug resistance mechanisms to PARPi involving *BRCA* mutation reversions and *ABCB1* fusions are well known but they are often not present in all tumour cells,[107,108] suggesting that multiple resistance mechanisms might be present within an individual patient. Research aimed at delineating novel resistance mechanisms is needed. Another area of investigation is the immune infiltration and tumour hypoxia,[109] and how modulating the microenvironment might prompt responses to therapy. Because preliminary results of immunotherapy as single agent showed low response rates in HGSOC,[110] novel approaches are based on combination strategy and T-cell therapy. [111]

Efforts are also ongoing to improve drug delivery; antibody-drug conjugates are an important class of highly potent biopharmaceutical drugs designed as a targeted therapy. Antibody–drug conjugates consist of an antibody designed against a specific target linked to a cytotoxic agent.[112] Because targets do not have to be drivers of tumour growth, antibody-drug conjugates are an emerging class of therapeutics, particularly in ovarian cancer without clear oncogenic drivers. As an example, Mirvetuximab soravtansine (IMGN853) consists of a humanised anti-folate receptor monoclonal antibody attached to the cytotoxic maytansinoid DM4.[113] This targeted therapy with IMGN853 is being assessed in the phase 3 trial for patients with folate receptor-positive platinum-resistant EOC. The antibody-drug conjugate strategy offers the possibility to investigate functional imaging based on the identification of the target and tissue analysis.[114]

The challenge is to define the appropriate combination and sequence strategy for a patient at a specific time and

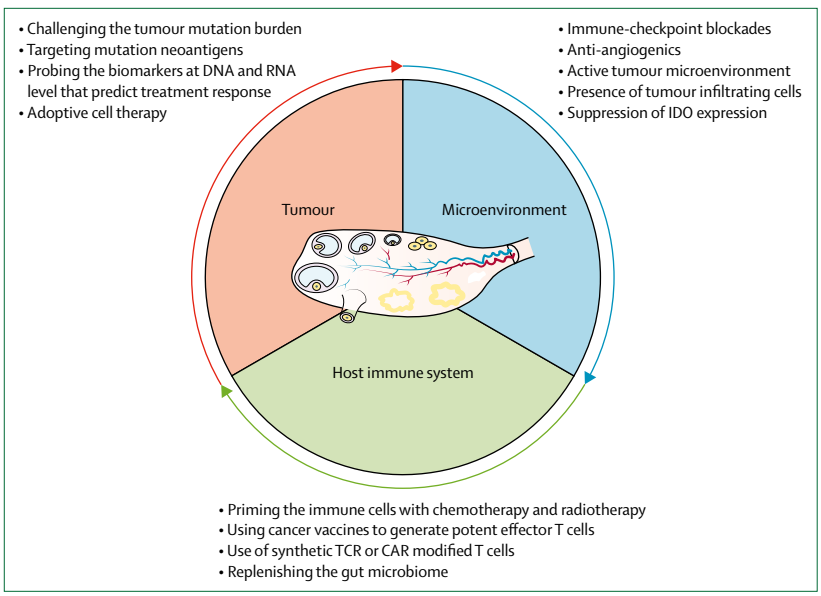

Figure 6: **Different immunotherapeutic strategies in targeting ovarian cancers**
This strategy ranges from targeting the ovarian cancer cells, or the tumour microenvironment, or boosting the host immune system. IDO=indoleamine-pyrrole 2,3-dioxygenase. TCR=T-cell receptor. CAR=chimeric antigen receptor.

then identify mechanisms of resistance that will guide the treatment tailored to each patient.

Patient journey: evolution of disease

In HGSOC, *TP53* mutation is followed by multiple sequential mutational processes that drive the pathogenesis into a highly complex, genomically unstable tumour with low frequency of oncogenic mutations and few recurrent copy number alterations.[115] These aberrations can evolve with time and exposure to different lines of treatment, increasing the risk of developing therapeutic resistance. Majority of targetable mutations are concordant over time, despite intercurrent chemotherapy and associated clonal selection.[116] However, reversion mutations restoring the open reading frame of *BRCA* have been described with PARPi treatment,[117,118] and recovery of BRCA protein expression,[119] which predict for resistance to therapy.[120] Whole genome sequencing has established the potency of the somatic genome, characterised with diverse DNA repair deficiencies that can be used to stratify ovarian cancers into distinct biological groups with predictive signatures of resistance or relapse.[121] Next-generation sequencing is further facilitating a deeper understanding of resistance and response; in particular, the analysis of exceptional responders in clinical practice allows for discovery of predictive signatures that might revitalise or reposition the use of targeted agents.[122] Unique genomic determinants might be associated with the exceptional outcome in HGSOC patients; concurrent homologous recombination deficiency and RB1 loss were associated with favourable outcomes, suggesting that co-occurrence of specific mutations might mediate durable responses.[123] Spatial and temporal intra-tumour heterogeneity is a major challenge for the development of precision medicine and treatment.[124–126] Several new targets have been identified for each tumour type and are under evaluation as part of clinical trials (figures 2–4). Given the complexity involved in the mechanisms of therapeutic resistance, the characterisation of the disease processes at recurrence is key to identify the best treatment strategy for a patient at that time (figure 5). Combination therapy targeting DNA damage response, cell cycle, signalling pathway, and tumour microenvironment might be required to control the profound genomic complexity of evolution of EOC. This combination therapy involves a change in practice and a need for sequential biopsy, or liquid biopsy, to define the mechanism of resistance involved in the current episode of recurrence. Studies have shown the feasibility to detect reversion mutations in circulating tumour DNA on resistance to therapy, suggesting its potential clinical use.[118,127] Circulating tumour cell collection has shown real-time molecular characterisation of drug response at multiple timepoints in some cancers.[128]

The cellular, molecular, and spatial heterogeneity of ovarian cancer has led to very active consideration of harnessing the immune system to target this disease (figure 6). Tumour infiltrating lymphocytes are associated with improved clinical outcome in EOC patients;[129–131] prognostic subtypes have also been suggested.[76,132] Early studies have incorporated interventions with immune checkpoint blockade, cancer vaccines, and adoptive cell therapy. Initial trials included all subtypes of EOC, and response rates appear to be modest with checkpoint inhibitors as single agent in HGSOC with some encouraging activity seen in clear-cell ovarian cancer.[133–136] Beyond the PD-1 and CTLA-4 pathways, additional tolerogenic mechanisms can be targeted and used in combination with immune therapies, such as chemotherapy or anti-angiogenics. The hypothesis that immune targeted therapy in combination with chemotherapy or molecular targeted agents will improve immune exposure of and activity of EOC has led to the emergence of many beforementioned combination options as well as randomised clinical trials in first-line and recurrent treatment settings.

Quality of life and symptom management

Given the potential chronicity of EOC, patients might experience a multitude of relapses and treatment-related adverse events that can affect quality of life. Efforts are ongoing to integrate this endpoint into clinical trials and design studies in recurrent disease in which the patient reported outcomes are major endpoints.[137] At the time of recurrence, the goal of treatment is to control the disease and maintain quality of life. This goal means that treatments have to ensure an acceptable safety profile and balance symptom benefit with risks, particularly in the platinum-resistant setting.[138] To incorporate a patient's perspective on

side-effects, patient reported outcomes have been integrated into standard reporting of adverse events based on Common Terminology Criteria for Adverse Events.[139,140]

Malignant bowel obstruction is the most common complication of EOC progression and is described by patients as the most devastating event experienced over their disease trajectory with a median survival of less than 5 months.[141] This complication is a major clinical challenge because of the few therapeutic options associated with substantial symptoms, such as the inability to maintain oral intake, vomiting, and abdominal pain, which lead to nutrient deprivation. Malignant bowel obstruction management is not well defined and includes potential surgical or radiology intervention, medical support, and the ethical dilemma of total parenteral nutrition. Efforts are ongoing to offer a multidisciplinary management including surgery, chemotherapy, radiation, interventional radiology, and to include patients' preferences.[142,143] In this setting, the question of total parenteral nutrition is difficult because the selection of patients who will benefit from total parenteral nutrition is not well described and the majority of patients will die from cancer progress, not starvation.[144] Early intervention of palliative care is also important to improve patient care.[145,146]

Conclusion

Efforts towards better understanding and characterising the different types of EOC have been leveraged into new therapies, transitioning to standard of care. Discovery research is advancing into hypothesis-driven trials and translational research. Access to clinical trials and international collaboration has been crucial in this progress, particularly for the rare tumour types. Building a strong multidisciplinary network with the integration of discovery research with clinical practice is key to improve precision medicine that will affect patient care. The delivery of value-based and patient-centred care is paramount in improving outcomes as is learning from each patient, from treatment responders to refractory patients. The value of cancer treatment is based on clinical benefit, toxicity, and improvements in patient symptoms or quality of life in the context of cost.[147] Patient engagement and input should be integrated to make these efforts meaningful and measurable.

Contributors

SL wrote the summary; introduction; the sections on HGSOC, future direction, disease evolution, and patient management; and had an editorial overview of the entire manuscript and revised it for final publication. CG wrote the rare histology subtype section of EOC, had an editorial overview of the entire manuscript, and provided expertise on the direction and management of ovarian cancer. IV wrote the part on surgical management of EOC and reviewed the manuscript. AMO did the seminar design and overview, provided scientific expertise, guidance, and support in the manuscript writing; reviewed all the data; and had an editorial overview of the entire manuscript.

Declaration of interests

We declare no competing interests.

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